A review on wound management with special reference to nanotechnology

Debosmita Datta, Raman Suresh kumar*
Department of Pharmaceutics, JSS College of Pharmacy Ooty, JSS Academy of Higher Education and Research, Ooty, Nilgiris, Tamil Nadu, India

ABSTRACT
Management of wound care mainly depends upon the advancement of innovative and effective wound care product to achieve speedy recovery and minimising scar formation. Wound healing management has been always an interesting field of research till date due to serious need for new wound treatment. Appropriate wound care is a significant challenge because of the complications associated with wounds as well as low permeability through the skin. The interconnected events of wound healing occur simultaneously to restore the tissue integrity and functions of the cells. Wound healing gets hampered by numerous factors. These physiological events occur easily in normal human being, but in some situations these molecular events are affected, resulting in hard to heal/ chronic wounds. In current years nanotechnology has emerged as an exciting field with several applications in skin regeneration. These nanoscale delivery systems have numerous benefits in the healing process such as decrease in drug's cytotoxicity, administration of poorly water-soluble drugs, better skin permeation, controlled release behaviour, antimicrobial activity, as well as stimulation of fibroblast proliferation and reduced inflammation. Thus, emerged as an effective strategy and approach for the treatment of chronic wounds. This review briefly discusses about the wounds, characteristics of an ideal wound dressings along with a special mention regarding the several strategies of wound healing by nanotechnology with their functions and advantages.

INTRODUCTION
Since day by day the number of chronic wound sufferers are increasing in the world, the market value of wound dressings is also increasing and expected to grow in dollars in coming years. (Das and Baker, 2016). Skin, the largest organ of the body has three different layers, which are self-renewable and have various functions and roles in maintaining tissue integrity and cellular functions (Metcalfe and Ferguson, 2007). It also provides protection from microbial invasion. Naturally wound can be healed because of the regenerative property of the skin. But sometimes, this property does not works perfectly leading to formation of chronic wounds and further brings risk in patient’s health. Thus, wounds can be classified into acute wounds and chronic wounds. Acute wounds usually heal in a predictable manner with no complications. The wounds which takes more than 12 weeks to heal is considered as a chronic wound. Delayed healing, prolonged inflammatory phase, Usually, wounds taking more than 90 days to heal are referred as chronic wounds (Saghazadeh et al, 2018). It is important to carry out all the four phases of wound healing like haemostasis,
inflammatory, proliferative and maturation phase to occur in correct manner in proper time. Chronic wounds occur due to metabolic disorders triggered by systemic diseases like diabetes, vascular insufficiency or obesity. Many deeper wounds do not heal perfectly, leading to scar formation at the wound site (Suri et al., 2007). Therefore, it is essential to develop an ideal wound dressing that can prevent bacterial penetration into the wound. The modified delivery approach should influence the different sequences of wound healing such as proliferation, migration and differentiation of cells and further helps in tissue regenerations. Nanoscale wound dressings are smart and innovative. Nanoparticles are capable enough to travel inside the cytoplasmic space by crossing over the skin barriers and also improve drugs biocompatibility, bioavailability. Nanomedicines signify a great opportunity to expand and improve currently available medical treatments, overcoming the drawbacks of the conventional treatments (Sandhiya et al., 2009). This paper will review on the currently available nanotechnology-based therapies along with its role and importance in the field of wound healing and tissue regeneration along with a brief idea about wound and healing phases.

Limitation Of Traditional Wound Care

Wound care dressings mostly depend on the dressing materials which can provide fast and effective healing of damaged tissue and protection from infections. Natural traditional materials are biodegradable, but they require frequent change of dressings as they absorb foreign materials and dead tissue. Synthetic traditional dressings are non-biodegradable (Petruptye, 2008). Moreover, traditional wound dressings are unable to prevent invasion of microorganisms. It provides a dry environment to wound. At the time of removal patient suffers pain since the dressings adhere to the wound bed. And it does not provide permeability to gases (Stashak et al., 2004).

Ideal Wound Dressing Characteristics

Selecting a wound dressing which can heal the chronic wound within a specific time period as well as can provide an optimum healing environment is what in a need for always. An ideal wound dressing should have the following characteristics which are summarized in Figure 1 (Kamoun et al., 2017; Sezer and Cevher, 2011).

Classification Of Wound Dressings

The wound dressings can be classified as of the following.

Based on nature of action

According to the nature of action, wound dressing materials are of the following types:

1. Interactive dressings – Polymeric biodegradable films and foams which are permeable to water vapour and oxygen.
2. Passive dressings – gauze
3. Bioactive dressings – An advanced type of dressing, capable to transport bioactive molecules to injured site. e.g., chitosan, collagen and alginites (Paul and Sharma, 2004).

Based on the dressing materials used

According to the nature of materials used, wound dressings are of the following types

1. Traditional dressings – gauze and gauze-cotton composite the most common traditional dressings. Despite of having many disadvantages it is efficient enough to provide physical support and microbial protection.
2. Biomaterial dressings – Biomaterial dressings are classified as follows

Derivatives of tissue – These are mainly collagen derivatives with less risk of contamination. But prone to get infectious on prolonged use.

Allografts – this is a way of transplantation with either fresh or frozen-dried skin residues. These have several limitations like more cost, hard to prepare, limited shelf life and donor deficiency.

Xenografts – Commercially available materials with easy sterilisation and longer shelf life.

3. Artificial dressings – The main reason behind this preparation is to overcome the limitation of the existing dressing. But the preparation of an ideal artificial dressing very difficult which will meet all the requirement for perfect wound healing (Gupta et al., 2010b; Sezer and Cevher, 2011).

Based on the formulations

Various pharmaceutical formulations have been formulated for the treatment of burns and wounds which are classified as follows

1. Gels – Gels are semi-solid viscous in nature, in which the organic and inorganic substances are dispersed. Hydrogels consists of water around 96%. Along with cross-linked insoluble polymers. They provide moist wound surroundings and helps to absorb exudate.
2. Films – Made up of one or more polymers by different methods and has good permeability for oxygen and water vapour but not foreign bodies.

3. Foam dressings – polyurethane foam dressing is mostly used as it absorbs wound exudate by maintaining a moist wound environment. These are semipermeable and highly absorbent dressings which provides protection to the skin and encourage healing. Silicone coated foam dressings are used for easy painless removal (Sezer and Cevher, 2011).

Advancement Of Wound Dressings From A Perspective Of Nanotechnology

A growing number of innovative strategies regarding nano therapies have emerged in the field of wound healing. Numerous nanoscale approaches were introduced to target various phases of tissue repair. Nano drug delivery system is preferred as it has vast potential in enhancement of drug therapeutic efficacy for their ability to prevent drug degradation and sustained release action. Various types of nano-strategies are available and can improve wound healing is further discussed in this article.

Need Of Nanotherapies In Wound Management

As previously mentioned, conventional topical delivery having some limitations and compromise safety and efficacy of the drug (Teichmann et al., 2007). To overcome the boundaries, a new drug delivery system is in need which will be potential enough to achieve unreachable goals and provide optimum effect without reducing the efficacy. Pharmacokinetic information also displays less absorption of drug molecule from conventional products. A new carrier system is the need of the hour which can efficiently improve penetration through skin and minimise the side effects of the drug topical application fails to achieve targeted action (Pople and Singh, 2011). The novel nano-drug delivery system can deliver drug to the targeted site. The nano vehicles deliver the drug in a localised manner by forming skin reservoirs (Bawarski et al., 2008). The nanoparticles have the ability of crossing layers of skin. The surface of the nanocarriers is negatively charged. The charge Skin acts as a negatively charged. surface charge of nanoparticles. The charge present on the surface of nanocarriers helps the drug to travel through the skin. In the following section, various nano technologies are described.

Classification Of Possible Nanotechnology In Wound Healing

The particle’s surface area increases exponentially by downsizing to nanometric range. Dynamic light scattering (DLS), Raman scattering (RS) and fluorescence correlation spectroscopy (FCS) provides information about the size distribution of nanoparticles, whereas circular dichroism (CD), Mass spectroscopy (MS) and Infrared spectroscopy (IR) helps to find their structure and surface characteristics. In addition, transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be an important investigational tool for studying the properties and dynamics of nanomaterials. Through
Polymeric nanoparticles

In the topical area polymeric nanoparticle have been gained an increased attention to overcome the limitations related to other lipid system. The limitations include lower drug loading capacity, higher drug permeation and phase stability issues. Many biodegradable, non-toxic synthetic or semi synthetic polymer have shown promising effect for topical delivery of drugs. This includes chitosan, polyactic acid (PLA), poly(ε-caprolactone), poly (lactic-co-glycolic acid) (PLGA) These polymeric carriers show good controlled and sustained release by modifying the composition of polymers. PLGA-based nanoparticles considered as the most useful because of their potent properties like less toxicity, biodegradability, biocompatibility and entrapment of drug molecules (Lin et al., 2014). PLGA is used for preparation of polymeric NPs and it is also approved by FDA (Shah et al., 2012). Fabrication of PLGA NPs are usually done by emulsifying different hydrophobic compounds, by organic solvents and surfactants (Chereddy et al., 2016). The drug permeation is higher in case of polymeric nanoparticle due to steady release of drug from nanoparticles on the skin surface. But it is unable to permeate deeper skin layers (Alvarez-Román et al., 2004). Researchers found that, PLGA was used to prepare EGF-loaded NPs, further used for wound healing. It showed maximum proliferation and reduce the time of healing (Luengo et al., 2006). In addition, chitosan (CS) acts as prophylactic agent to prevent spreading of infections. It is a polysaccharide with numerous significant biopharmaceutical characteristics and it acts as penetration enhancer in topical formulations. Chitosan-based PLGA nanoparticles can advance the topical delivery in several ways, like increased stability of the macromolecules. Two drugs can be incorporated in outer and inner layers of the nanoparticles. The free amino group of chitosan helps to conjugate with other molecule and thus acts as penetration enhancer (Dai et al., 2009). In some research studies it is found that CS NPs were used in the preparation of films and various bandages to give more mechanical support to wound as well as to treat infected open wounds (Huang et al., 2011).

Nanoemulsions

Nanoemulsions (NE) are the mixture of two immiscible liquids which are stabilised by addition of surfactant. The nanoparticles formed are of size range of 20–200 nm (Jaiswal et al., 2015). Compared to microemulsion nanoemulsions have more loading capacity for lipophilic active ingredients, which can be beneficial for topical application. The aqueous phase consists of water and cosurfactants e.g. ethylene glycol and glycerine. High pressure homogenization energy micro fluidization and ultrasonication are few methods a to prepare nanoemulsions (Mason et al., 2006). The antimicrobial oil-in-water nanoemulsions is efficient against bacterial pathogens and show broad spectrum activity due to the less droplet diameter (Sugumar et al., 2013). In one case, a nanoemulsion was formulated with chlorhexidine acetate which showed efficacy against a methicillin-resistant S. aureus (MRSA) in infection wound model. And nanoemulsion showed effective result against MRSA. In another study, Eucalyptus oil nanoemulsion based film was produced which exhibited a better antibacterial effect against S. aureus. And it was found to be non-irritant and had wound healing efficacy (Chandrasekaran et al., 2015).

Liposomes

Liposomes have been considered as a potential carrier of drugs and biologically active components. These are spherical vesicles, made up of one or more lamellar lipid bi-layers, and capable to carry a range of drug potentially. Both lipophilic and water-soluble substances can be encapsulated in liposome. It is ideal for topical delivery as their lipid composition is quite alike to epidermis which further helps them to cross the epidermal barrier. In addition, liposomes are considered to be nontoxic as well as biodegradable. Liposomes are expert to localize the effect of the drug by dermal accumulation and drug reserve formation. Almost all kind of therapeutic ingredients can be incorporated into liposomes. According to studies liposomal gel plays an effective role in delivering the drug through the skin as it delivers the therapeutic moiety in a controlled release manner by forming localized drug-depot (Gupta et al., 2010a). Nano-liposomal formulations have better penetration capability of several entrapped agents through skin. In 1980 Mezei and Gulasekharam made the first study on liposome in topical application (Mezei and Gulasekharam, 1980). One case study said that dihydroquercetin loaded liposome has been formulated, which improved the antioxidant property and reduce the necrosis burned area, and leads to better...
wound healing of the skin (Naumov et al., 2010).

**Hydrogels**

Hydrogels are three-dimensional, hydrophilic, polymeric networks. They can absorb aqueous fluid in large amounts. They play a key role in tissue regeneration because of their highly porous nature and soft consistency (Caló and Khutoryanskiy, 2015). Hydrogels provide a non-adhesive cooling effect. It is considered as an ideal wound dressing material. The components like chitosan, PEG, PVA, dextran, antibiotics when combined with hydrogel NPs induces tissue regeneration in burn models. In one study hydrogel loaded with tetracycline hydrochloride was used, which exhibited an antimicrobial effect against both Gram-negative and Gram-positive bacteria, and scarring was also less (Anjum et al., 2016).

Similar to natural biological ECM a 3D network like hydrogel incorporated matrix has been formulated which allows more cell growth (Ahmed, 2015). The nanoplatforms help to release several bioactive molecules like growth factors and antibacterial agents. Recent study showed gelatin-based hydrogels which transport basic fibroblast growth factor (bFGF) induces healing without scarring (Kobayashi et al., 2017).

**Lipidic nanoparticles**

Lipid nanoparticles are of two types - Solid lipid nanoparticles (SLNs) and nanostructured lipid nanoparticles (NLCs). These are the topical drug delivery vehicles which can be delivered oral, inhalational and parenteral routes. The lipidic nanoparticles consider as an outstanding tool to deliver drugs in dermatological fields (Jensen et al., 2011). SLNs consist spherical solid lipids with hydrophilic moieties such as PEG derivatives, stabilized by different surfactants. NLCs are the improved generation of SLNs, which consists of both solid and liquid lipid components. On addition they are having better drug loading capacity as well as better stability (Müller et al., 2016). NLCs can overcome the limitations associated with SLNs such as limited drug loading, drug leakage during storing, and risk of gelation. The lipid core has more biocompatibility and biodegradability. And they are potential enough to deliver the active ingredient in a controlled manner. Lipophilic drugs can be easily delivered by NLCs into damaged wound tissues (Sivaramakrishnan et al., 2004). Additionally, the nano size gets closely connected to layers of skin and helps in better drug permeation. Hence, these carriers act as a key tool to deliver the drug over an extended period of time with reduced side effects (Narang et al., 2015).

Many studies have been performed regarding the efficacy of these nanoparticles on dermal delivery. The types of the lipid used for the preparation influence the penetration profile of the drug, and correlates with drug solubility and lipid polarity. A poorly water-soluble antifungal drug named Miconazole encapsulated in NLCs which showed better antifungal action against candidiasis (Mendes et al., 2013). In another recent study it was found that the NLCs loaded with emulsified recombinant human (rh)EGF-loaded stimulated fibroblast expansion and production of collagen and thus induced wound healing (Gainza et al., 2015).

**Inorganic nanoparticles**

1. **Silver**

Silvers are well recognized for their potent bactericidal activity and is generally used in the treatment of burns. Nowadays several forms of silver coated dressing material are available which can effectively distribute the biologically active molecules and thus for effective distribution of the drug, thus plays an efficient role in chronic wound management, (Hamdan et al., 2017) Silver nanoparticles (AgNPs) based dressings can be used for prolonged period of time and AgNPs are more effective in less concentration. The AgNPs can modulate release of anti-inflammatory cytokine which promote rapid wound healing. Combination of AgNPs and collagen synergise the antibacterial activity and thus forms an ideal wound dressing material (Yildirimer et al., 2011). Among all the metal nanoparticles AgNPs is mostly used in the formulation development for burns, wounds because of their several potent properties. AgNPs successfully reduce biofilm formation interrupts quorum sensing followed by detoxification of the bacterial toxins. The acidic environment under in vivo conditions, oxidises AgNPs to silver ions. The generated silver ion inhibits Adenosine triphosphate (ATP) production, thus shows antibacterial property. Biocompatible material combined with AgNPs are used as wound dressings which exhibit better proliferation of keratinocyte at the wound site. In one study MADO-AgNPs (dopamine meth acrylamide-co-methyl methacrylate) (MADO) was used, which efficiently inhibits the growth of P. aeruginosa i, S. aureus, and E. coli (Liu et al., 2010).

It also increases epithelization with complete healing within short time whereas there was an incomplete healing in untreated group. Ag/AgCl nanomaterial produce a huge number of oxidative free radicals along with the release of silver ions. It is capable enough to fight against gram-positive as well as gram-negative bacteria. Moreover, it enhances reepithelialization in mice burn model, thus speed up the wound closure (Vijayakumar et al., 2019).
Mechanism of Action of Silver Nanoparticles

The main mechanism of AgNPs is firstly they will attach with the bacterial cell membrane will create sulphuric and phosphoric bond with either protein of bacterial cell membrane or thiol groups of various enzymes, specially which are involved in the respiration leading to apoptosis (Sondi and Salopek-Sondi, 2004). The AgNPs will transform to a low molecular weight area once it has entered into bacterial cell. The nanoparticles can interfere with DNA synthesis during cell division which exhibit and enhance bactericidal activity (Vijayakumar et al., 2019). In one study it was observed that silica adhere firmly to open wounds. So AgNPs integrated into silica nanoparticles via the support of disulphide bonds (Ag-MSNs), the novel compound showed excellent antibacterial property with less cellular toxicity (Naraginti et al., 2016).

2. Gold

Gold nanoparticles (AuNPs) are considered to be as an ideal option for wound therapy due to their good chemical stability and comparatively easy to synthesize. Moreover, AuNPs act as an as antioxidants, improving the healing process. The activity of AuNPs significantly increases when polymers or stem cells are incorporated. Chitosan-AuNP is a biocompatible material which increases scavenging of the free radicals. In one research study on rat wound model chitosan-AuNPs effectively improve haemostasis, re epithelisation and faster wound healing rate. Though lower concentration of AuNPs enhance wound healing but higher concentration is associated with cytotoxicity (Lu et al., 2010).

Mechanism of Action of gold nanoparticles

Gold nanoparticles show their anti-bacterial activity mainly by two mechanisms. 1) AuNPs inhibits the enzyme ATP synthase as it enters into the bacterial cell., which further lowers the ATP levels and ultimately results in cell death due to downfall in energy metabolism. 2) AuNPs are also effective against multiple drug resistant organisms through ROS (reactive oxygen species) independent mechanisms (Pati et al., 2014).

3. Zinc Oxide

Zinc oxide (ZnO) is a stable inorganic bactericidal agent. Zinc is an essential chemical element for wound healing specially in chronic wounds. The topical application of zinc has a potent role in reducing inflammation and improving re-epithelialization and regeneration of extracellular matrix. The efficacy of zinc oxide nanoparticles depends on the concentration and size of the particles. Additionally, zinc also acts as a supervisor for auto-phagocytosis and migration of keratinocytes which are serious for tissue repair. By a two-step process Zn ion gets released from the ZnO nanomaterial. Hydrated ZnO which forms by the reaction between those ions and biological fluid, acts as a bactericidal agent. However, their usage in wound healing gets limited due to high intrinsic toxicity. The high concentrations of ZnONPs leads to mitochondrial dysfunction in keratinocytes, which induce the release of lactate dehydrogenase. Likewise, ZnONPs forms reactive oxygen species leading to cell membrane oxidative stress and apoptosis. Moreover, it was found that ZnONPs generate carcinogenic alterations (Yang et al., 2009). ZnONPs Nano composite exhibits anti-biofilm and antibacterial effects against Staphylococcus aureus and methicillin resistant Staphylococcus haemolytic us, through the reactive oxygen species release (Gao et al., 2017).

Nanofibers (NFs)

Nanofibers (NFs) are usually engineered from natural as well as synthetic substances. Nanoscale NFs augment drug interaction with scaffolds and thus use in tissue modelling as well as to deliver antimicrobial drugs. NFs of 5nm diameter can perfectly match the collagen in all forms, exists in ECM thus NFs are widely used as nano materials in wound care. NFs are able to fabricate with various pore size, density and diameter (Hromadka et al., 2008). Electrospinning, the most accepted technique to produce biodegradable NFs. An electrically charged liquid of substrate is to instilled into a fast-rotating collector. By the help of electrostatic charge imbalance, the NFs are fabricated which reduce the surface tension of the liquid and evaporates the solvent (Hu et al., 2014). NFs can efficiently transfer various molecules like anti-cancer drugs, antibacterial agents, nucleic acid and various growth factors. Mostly electro spun NFs has been used in the form of scaffolds in tissue industry. Copper can be incorporated as it helps in collagen fabrication and fibrinogen stabilization. Thermally induced phase separation (TIPS) also can be used for fabricating NFs. In one study TIPS methods was used to generate a silk fibroin -PLGA NF scaffold. This showed more water vapour absorptivity, ratio of water uptake rate/loss rate (i.e. the absorption of humidity from wound skin to limit wound infection and fortification of wound skin). Moreover, sustained release of the drug has been also reported (Liu et al., 2016). Shape memory polymer–based NFs can be also fabricated to prepare smart wound dressings which can be applied to regenerate skin in chronic wounds (Mohtaram et al., 2017). In one study a multifunctional electro spin based NF was generated for wound healing. NFs has been manufactured from.
gelatine, shape-memory polyurethane and chitosan which had higher anti-bacterial activity against E. coli and P. aeruginosa (Tan et al., 2015).

Films

The film is defined as a similar structure with even characteristics that may consists of different kind of polymers. Films have been used widely since past for wound healing. It can be used as primary as well as secondary dressings. Sometimes other materials like hydrogels, foams, composite dressings are incorporated. (Matthews et al., 2005) these dressings were manufactured from nylon derivatives. But it has many limitations like it failed to allow for exudates absorptions and thus supports bacterial contaminations. Modified films are made up of natural polymeric material like chitosan and collagen which are biocompatible as well as biodegradable. Modern films are transparent semi permeable in nature which maintains a moist wound environment and thus promotes cell migration and autolysis of necrotic tissue. It also protects from bacterial contaminations. The properties of the film include it allows visual check and adhere only to skin not to wounds. It is good for secondary dressings and low infected wounds. Engineered films are considered as a promising material for tissue engineering. In literature survey many reports have been published regarding role of films in wound healing. For example, curcumin loaded chitosan film (Mayet et al., 2014).

Nanofibrous Scaffolds

The primary aim of tissue engineering is the creation of a biocompatible and biodegradable scaffold combining with living cells and bioactive moieties. A Scaffold is a network like structure which supports the living tissue and replace, regenerates and repairs affected tissues. The ideal activity of scaffold is to mimic the biological as well as structural properties of ECM (Chung and Park, 2007).

In case of chronic wounds, tissues are unable to regenerate by themselves thus concept of scaffold is needed which will promote the natural healing. Simple electrospinning technique has been used to produce morphologically similar nanofibrous scaffold to ECM. The electro spun nanofibers have large surface area and porosity which helps in better permeability for oxygen and water. Additionally, it is capable to adsorb extrudes and parallelly protects the affected area from bacterial invasion. The electrospinning technique can be used for both degradable nanofibers like chitosan and collagen as well as nondegradable polymer fibres such as polyvinyl alcohol (PVA). Surface functionalisation of a scaffold may promote adhesion of cells by interacting with particular cell matrix. Immunologically active ingredients and many growth factors can be incorporated within the scaffold. The ideal scaffold should have some features such as (1) the optimum shape which can provide mechanical support (2) minimisation of immune and inflammatory responses (3) an interconnected highly porous scaffold allows optimal tissue growth (Khil et al., 2003). Application of nanotechnology and use of nanomaterials for fabrication of biodegradable scaffold induces more tissue regeneration and promotes wound healing faster.

CONCLUSIONS

In recent years, nanotechnology has been in a limelight and has experienced an upward expansion. The moreover the knowledge regarding the molecular events involved in wound healing has reached to a different level which further excites the researchers to formulate new nano therapeutic strategy which can directly act on cellular and sub cellular level in wound healing process. Nanotechnology successfully overcomes the limitation and the barriers associated with the available conventional treatments for wounds. Nanoparticles based delivery system can be more valuable to enhance the therapeutic power of biological molecules. Different types of elements like growth factors, anti-bacterial agents and anti-inflammatory agents can be incorporated to formulate a more potent wound dressing. Nanoparticle based wound materials show site specific action as well as drug loading capacity is more.

In this review different types of nanoparticle based wound healing therapies has been described which may further help in the future in the field of wound healing management. This review aim to provide an overview to develop an ideal wound dressing which will be capable enough to overcome all the limitation and challenges existing now. Various nanotechnologies and their role in wound healing have been briefly described in this article which may further be helpful in designing the wound care product with optimum and targeted action in managements of wounds.

Conflict of Interest

None.

Funding Support

None.

REFERENCES


Sezer, A. D., Cevher, E. 2011. Biopolymers as wound


